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## EDITORIAL COMMENT

# Postmenopausal Hormones and Heart Disease*

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Multiple observational studies have reported that postmenopausal women who use estrogen have a lower rate of coronary heart disease (CHD) events than women who do not use estrogen (1). Meta-analyses of these epidemiologic findings suggest a 35% to 50% reduction in risk of coronary disease among women using estrogen compared to nonusers (2,3). These findings are supported by plausible biologic mechanisms including a beneficial effect of estrogen therapy on low-density lipoprotein and high-density lipoprotein cholesterol (4), improved endothelial function (5) and less progression of atherosclerosis in animals (6). Thus, it was very surprising when the results of the first large trial of the effect of postmenopausal hormone therapy on risk for coronary events showed no benefit of treatment.

The Heart and Estrogen/progestin Replacement Study (HERS) was a randomized, blinded, clinical trial among 2,763 postmenopausal women with documented coronary disease and a uterus; they were randomly assigned to receive daily conjugated estrogen plus medroxyprogesterone acetate or placebo. After an average of 4.1 years of follow-up, there was no difference between the groups in the primary composite outcome of nonfatal myocardial infarction (MI) and coronary death or any of several secondary cardiovascular outcomes (7). Even more surprisingly, HERS investigators found that women assigned to estrogen plus progestin had a 50% increased risk of coronary events in the first year of the trial. Within the first year, the risk was highest in the first four months (relative hazard 2.3; 95% confidence interval 0.9–5.6). This increased risk returned to baseline over the subsequent two years, and risk appeared to be lower in the hormone-treated group than in the placebo group beginning in the third year of the trial. The early increase in CHD risk observed in the HERS trial may have occurred by chance or may be due to some adverse effect of hormone therapy. To decide between these alternative explanations, repetition of the HERS findings would be helpful.

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This issue of the *Journal* contains a report from the Coumadin Aspirin Reinfarction Study (CARS), a randomized, blinded trial to test the effect of low-dose aspirin plus low-dose warfarin compared to standard aspirin therapy for the prevention of cardiovascular events in persons with a recent MI (8). The CARS trial enrolled 8,803 participants 3 to 21 days after documented MI. The trial was stopped after a median of 14 months of the planned two years of follow-up because therapy with low-dose aspirin plus warfarin was no more effective than standard aspirin monotherapy. In this issue of the *Journal*, Alexander et al. (9) used data from the 1,857 postmenopausal women enrolled in CARS in an observational cohort design to evaluate the effect of initiation of hormone therapy on risk for coronary events. Women who began hormone therapy after their MI had a higher subsequent incidence of unstable angina than women who had never used hormones (39% vs. 20%; $p = 0.001$). Interestingly, however, new hormone users suffered death or recurrent MI at a *lower* rate than never-users (4% vs. 15%; $p \leq 0.05$). Follow-up was relatively short (median 14 months; maximum 33 months), but there was no evidence that the higher rate of unstable angina observed among new users compared to never-users decreased over time.

These results differ in important ways from the results of the HERS trial. In HERS, it was risk for recurrent MI or coronary death that increased 50% in the first year of treatment, and there was no clear evidence for any early or overall effect on angina. In CARS, risk levels for recurrent MI and death were *lower* among new users of hormone therapy, and the rates of angina were doubled. These differences in results presumably reflect the crucial difference in design between CARS and HERS: HERS was a randomized trial of the effect of hormone therapy and CARS was not. The report in this issue of the *Journal* on the effect of hormone therapy is an observational analysis that used the CARS data in a prospective cohort design. Many important baseline differences existed between new hormone users and never-users in CARS. Statistical methods were used to adjust for these measured differences, but there is no way to adjust for unmeasured differences that can have a major effect on the outcome (10,11).

Although data from the CARS analysis provide little support for the HERS findings of early increased risk of MI and death associated with hormone therapy, preliminary data from another very large randomized trial are consistent. The Women's Health Initiative (WHI) randomized trial includes approximately 27,000 women without coronary disease who were randomized to receive estrogen plus a progestin or placebo if they had a uterus, and estrogen or placebo if not. The trial is now in approximately the third year of a planned nine-year treatment period. Recently,

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investigators in the WHI issued a press release and wrote letters to participants stating that they had observed an increased risk of cardiovascular events among the hormone-treated women in the first two years of the trial (12). Although no quantitative risk estimates were given, these results would not have been released in this fashion had they not been substantial. Hormone therapy appears to be having the same early adverse effect on coronary risk among these healthy women as among women in HERS with documented coronary disease. Final results of the WHI are not scheduled to be available for approximately four years. Although the participants were men and the dose of estrogen was high, the Coronary Drug Project also found that estrogen therapy after MI produced a pattern of early increase balanced by later decrease in new CHD events that closely resembled the findings of HERS (13).

If postmenopausal hormone therapy causes an increased risk of cardiovascular events early after starting therapy, what is the etiology? Both HERS and CARS investigators suggest that estrogen may cause thrombosis, arrhythmia or ischemia. The increased risk might decline over time if only a subset of users are susceptible to the adverse effect, or if users develop some form of tolerance over time.

In an effort to identify women at risk of the adverse effect, the HERS investigators examined multiple subgroups and found that women with baseline lipoprotein(a) [Lp(a)] below the median had a marked increase in risk of CHD events in the first year of treatment with hormone therapy (relative risk 2.1 compared with placebo; $p \leq 0.05$) and no benefit thereafter (14). In contrast, HERS participants with baseline Lp(a) above the median had less early harm and more overall benefit ($p = 0.04$). However, these findings are post hoc and might have occured by chance as nearly 100 possible subgroups were evaluated.

Because hormone therapy increases risk for venous thrombosis substantially (15), many investigators have assumed that an early adverse effect of hormone therapy is likely to be thrombotic. The effects of estrogen on coagulation factors are mixed, but reported procoagulant effects include increases in factors VII and X and protein C, and decreases in antithrombin III (16). Estrogen also increases levels of C-reactive protein (17,18), which is associated with inflammation, coronary plaque instability and possibly thrombosis (19). Psaty et al. (20) have reported observational evidence that hormone treatment is more likely to cause MI in women who have the prothrombin 20210 G-A variant and hypertension. These theories are plausible, but currently there is no firm evidence to support them. The HERS investigators are undertaking nested case-control studies to evaluate subgroups of women defined by several serum markers of coagulation and inflammation, but results are not currently available.

Although uncertainties still exist about the early increase in cardiovascular risk associated with postmenopausal hormone therapy, the overall message from the available clinical trials is clear. The HERS trial found no benefit of four years of treatment with postmenopausal hormone therapy in women with prior CHD (7). The Estrogen Replacement in Atherosclerosis (ERA) trial found that neither estrogen alone nor estrogen plus progestin was different from placebo in the effects on progression of coronary disease measured angiographically (18). A recent meta-analysis of small randomized trials of short-term hormone treatment also found no benefit (21). *No* randomized trial of hormone treatment has found reduced risk of cardiovascular events among postmenopausal women.

Randomized trials *have* established that hormone treatment causes a threefold increased risk of venous thrombembolism (15), and observational studies suggest that it may increase the risk of breast cancer after many years of treatment (22). In light of these adverse effects, and of the many proven approaches to preventing CHD in high-risk women (23,24), it seems clear that postmenopausal hormone therapy should not be used for the purpose of preventing coronary disease unless future data from well-designed randomized trials document such benefit.

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